Sound discrimination in left-hemisphere stroke patients with aphasia as reflected by mismatch negativity (MMN) and behavioral indices

Doctoral dissertation

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To Jere

Contents

Abstract

Sound discrimination in left-hemisphere stroke patients with aphasia as reflected by the mismatch negativity (MMN) and behavioural indices

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Effects of left-hemisphere stroke on auditory discrimination were studied. Auditory event-related potentials (ERPs) and behavioural discrimination abilities were compared between left-hemisphere stroke patients with aphasia and control subjects. For this purpose, research paradigms to measure auditory ERPs were developed. Furthermore, changes in the cortical substrate of auditory discrimination were followed up during recovery from a left-hemisphere stroke by recording the mismatch negativity (MMN) component. The results suggested that left-hemisphere stroke impairs automatic and active sound discrimination, and that, at least in some cases, the cortical discrimination impairment can be more precisely determined with the MMN than by using behavioural measures. The results also showed that the MMN reflects the recovery of sound discrimination after stroke onset with the alleviation of aphasia. Thus, the MMN provides a promising tool for evaluating and following up the recovery of central auditory stimulus processing in clinical studies.

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List of original publications (I-V)

This thesis is based on the following original articles, which are referred to in the text by their Roman numerals.

I
Joutsiniemi, S.-L., Ilvonen, T., Sinkkonen, J., Huotilainen, M., Tervaniemi, M., Lehtokoski, A., Rinne, T., & Näätänen, R. (1998). The mismatch negativity for duration decrement of auditory stimuli in healthy subjects. *Electroencephalography and Clinical Neurophysiology*, 108,154-159.

II
Tervaniemi, M., Ilvonen, T., Sinkkonen, J., Kujala, A., Alho, K., Huotilainen, M., & Näätänen, R. (2000). Harmonic partials facilitate pitch discrimination in humans: electrophysiological and behavioral evidence. *Neuroscience Letters*, 279, 29-32.

III
Ilvonen, T.-M.., Kujala, T., Tervaniemi, M., Salonen, O., Näätänen, R., & Pekkonen, E. (2001). The processing of sound duration after left hemisphere stroke: event-related potential and behavioral evidence. *Psychophysiology*, 38, 622-628.

IV
Ilvonen, T., Kujala, T., Kozou, H., Kiesiläinen, A., Salonen, O., Alku, P., & Näätänen, R. (2004). The processing of speech and non-speech sounds in aphasic patients as reflected by the mismatch negativity (MMN). *NeuroScience Letters,* 366, 235-240.

V
Ilvonen, T., Kujala, T., Kiesiläinen, A., Salonen, O., Kozou, H., Pekkonen, E., Roine, R., Kaste, M., & Näätänen, R. (2003). Auditory discrimination after left-hemisphere stroke: a Mismatch Negativity follow-up study. *Stroke*, 34, 1746–1753.

1. Introduction

1.1. Ischaemic stroke

Brain strokes are classified as haemorrhagic or ischaemic. Ischaemic strokes account for 80% of all strokes (Sudlow and Warlow, 1996) and are caused by either an embolism (e.g. coronary embolism) or thrombosis. Infarction of the middle cerebral artery (MCA) is the most common form of ischaemic stroke (Rordorf et al., 1998).

Loss of neuronal electrical function occurs when blood flow falls from the normal 50 ml to below 20 ml / 100 g brain / minute (e.g., Davenport and Dennis, 2000). A brain area which has reached this potentially reversible stage is called the penumbra. Irreversible damage occurs to brain tissue within minutes if blood flow falls below 10 ml. At this stage, rapid biochemical changes cause failure of cellular ion homeostasis, leading to cytotoxic (cellular) oedema in minutes to hours. Generalized slowing in electroencephalography (EEG) can also be observed (Fishman, 2000). Loss of cellular ion homeostasis finally leads to neuronal death after 3-4 minutes, with irreversible brain damage taking place after 5 minutes of deprivation (Mora and Bornstein, 1998). Several hours to days after an acute occlusion, brain capillary endothelial cells increasingly leak macromolecules, causing a state known as vasogenic oedema. Focal slowing of the EEG and disturbances of consciousness can be observed during this stage (Fishman, 2000). Usually after arterial occlusion, patients suffer from both cytotoxic and vasogenic oedema, together termed ischaemic brain oedema (Fishman, 2000), being maximal 1-3 days after the ischaemic event (Rosenberg, 1999). Pre-acute oedema is resolved within 2 weeks (O'Brian, 1995).

A condition called diaschisis, which is the loss of function and electrical activity caused by cerebral lesions in areas that are remote but neurally connected to the lesion (first introduced by von Monakow, 1914; see, for example, Mora and Bornstein, 1998, pp. 174-175), has been suggested to remain unchanged over the first 3 months after stroke onset despite clinical recovery (Infeld et al., 1995). Further, diaschisis after an MCA infarct has been shown to correlate with neurological severity (Infeld et al., 1995). Results from positron emission tomography (PET) studies indicate that a relationship exists between the resolution of diaschisis and subsequent recovery from a stroke (Cappa et al., 1997; Seitz et al., 1999).

The deficits due to a MCA area infarction depend on the location of the lesion and the extent of the area involved (Mora and Bornstein, 1998). Infarction may involve only the territory supplied by a single division or a small cortical branch. MCA infarct often leads to motor problems affecting the face, mouth, and other articulators. Infarcts involving the anterior part of the MCA impact the frontal and anterior parietal lobes, commonly producing different kinds of contralateral paralyses, as well as contralateral sensory disturbances. Infarcts causing lesions in the left hemisphere may create non-fluent aphasias such as Broca's aphasia, motor aphasia, and transcortical motor aphasia (see below). Disturbances in verbal memory also occur frequently. Infarcts in the posterior MCA area usually produce deficits without motor or sensory problems, but visual field cut is common. Lesions in the left hemisphere may cause Wernicke's, transcortical sensory, and conduction aphasias (Mora and Bornstein, 1998).

1.2. Classification and diagnosis of aphasias

Aphasia can be defined as a disturbance of previously intact language ability caused by a focal brain lesion, typically by vascular damage to the language-dominant cerebral hemisphere (Darley, 1982). There are a number of systems to classify aphasias, but the most commonly used in clinical practice is the Boston Classification System, in which disorders are classified according to the patient's comprehension, fluency, and repetition abilities (Goodglass and Kaplan, 1983; Table 1).

The Boston Diagnostic Aphasia Examination (BDAE) was designed by Goodglass and Kaplan (1983). According to the authors, the aims of this examination are to diagnose the presence and type of aphasic syndrome to identify thr cerebral lesions involved, to measure the level of performance, and to determine the resources and problems of the patient to guide the therapy. The BDAE was primarily designed for the sampling of language behaviours, which are discriminative in identification of aphasic syndromes. It is a relatively comprehensive battery, containing 27 subtests divided into the following 5 sections: conversational speech, auditory comprehension, oral expression, understanding written language, and writing. When a symptom pattern indicative of a syndrome is apparent from the test results, the probable site of the brain lesion may be inferred. It can discriminate between the different types of aphasias based on their typical characteristics. The BDAE has also been standardized in Finnish (Laine et al., 1997).

Another popular test in clinical use is the Token Test. It was first designed by Spreen and Benton (1969) to assess the verbal comprehension of commands. The shortened form of

the Token Test was introduced by deRenzi and Vignolo (1962). It includes 36 subtests divided into 6 sections increasing in complexity.

Table 1. Typical features of aphasias according to the Boston Classification System.

Aphasia type	Comprehension	Fluency	Repetition
Broca's	Good	Non-fluent	Poor
Transcortical motor	Good	Non-fluent	Good
Conduction	Good	Fluent	Poor
Anomic	Good	Fluent	Good
Wernicke's	Poor	Fluent	Poor
Transcortical sensory	Poor	Fluent	Good
Global	Poor	Non-fluent	Poor

Auditory comprehension is presumed to be rather intact in Broca's, transcortical motor, anomic, and conduction aphasias. Proper auditory comprehension requires perception of auditory stimulation, discrimination and identification of phonemes, and identification of words. In later stages of auditory comprehension, auditory short-term retention of words and sentences, identification of semantic meaning and further processing of syntax take place.

Broca's aphasia occurs due to lesions in the left inferior frontal areas as well as in subcortical white matter (Brodman's areas 45 and 44; Goodglass and Kaplan, 1983; Andrews, 2001). Speech is characterized as slow, hesitant, and telegraphic, and it is often associated with verbal apraxia (Andrews, 2001). In *transcortical motor aphasia*, resulting from a communication break between the pre-motor and supplementary motor areas (Brodman's area 6), lesions are typically superior and anterior to Broca's area. In this aphasia type, difficulties appear in initiating and maintaining conversation. Little or no paraphasias appear, articulation is good and auditory comprehension is rather intact (Goodglass and Kaplan, 1983). In *transcortical sensory aphasia,* speech is fluent and well articulated but may include neologisms. Comprehension is usually impaired due to lesions adjacent to Wernicke's area, the left posterior temporoparietal area (Goodglass and Kaplan, 1983). In *conduction aphasia*, speech is paraphatic, although it has a normal rate. This aphasia type is caused by lesions in the insula, the superior regions of the gyrus supramarginalis, and the primary auditory area (Brodman's areas 7, 40 and 42; Damasio 1981; Goodglass and Kaplan, 1983). Repetition is good in both transcortical aphasia types, and this ability is often used to separate these aphasias from other aphasias. In *anomic aphasia*, naming or word-finding problems are the major

features. The lesion is often in the temporoparietal area (Goodglass and Kaplan, 1983). In *Wernicke's aphasia*, speech is fluent and well articulated but includes neologisms and paraphasias. The main problem is in comprehension, which can be severely impaired. Lesions in the left superior temporal gyrus (Brodman's area 22) and sometimes in the inferior parietal lobule, including the supramarginal and angular gyri (Brodman's areas 39 and 40; Damasio, 1981), are the main causes of this aphasia type. *Global aphasia* results from lesions in multiple brain areas: the entire perisylvian region, both Broca's and Wernicke's areas, and the arcuate fasciculus (Goodglass and Kaplan, 1983). Speech comprehension, production, and repetition are all problematic for the patient.

1.3. Effect of left-hemisphere stroke on auditory perception

The left hemisphere is predominant in processing rapid acoustic changes associated with language functions (Efron, 1968; Swisher and Hirsh, 1974; for an overview, see Nicholls, 1999). Behavioural tests have shown that patients with lesions in the left temporoparietal and frontotemporoparietal regions are impaired in discriminating and sequencing verbal and non-verbal auditory stimuli (Tallal and Newcombe, 1978; Steinbüchel et al., 1999). Left-hemisphere lesions cause impairments in the processing of temporal but not spectral information in speech (Robin et al., 1990). Steinbüchel et al. (1999) showed that aphasics with lesions in the left posterior areas reaching the central sulcus have difficulties in auditory temporal-order judgments as compared with non-fluent aphasics with left-hemisphere lesions in the anterior regions. The authors concluded that sequential processing in the range of some tens of milliseconds is predominantly controlled by the left posterior cortex, which is also involved in language processing.

Pitch is an important feature in understanding the emotional content of speech. The processing of pitch changes, which convey emotional contours, appears to be lateralized to the right hemisphere (Zatorre et al., 1992; Basso, 1993). The perception of pitch may be impaired in patients with right-hemisphere lesions, while it may be unaffected in patients with left-hemisphere lesions (Alcock et al., 2000). Right-hemisphere lesions also cause problems in perception and production of emotional prosody (Bowers et al., 1987), which partly depend on the pitch-processing ability.

1.4. Language recovery after stroke

Significant spontaneous language improvements are common in the first 1-3 weeks after stroke onset, when the brain is recovering from the acute ischaemia (Pedersen et al., 1995; Mora and Bornstein, 1998). After this early phase of stroke, the greatest amount of improvement occurs within the next 3-6 months, as shown by several studies using a variety of aphasia tests (Kertesz and McCabe, 1977; Demeurisse et al., 1980; Lenderm & Lincoln, 1985; Kertesz, 1988; Mazzioni et al., 1992; Ogrezeanu et al., 1994; Laska et al., 2001). Enhancement in electrical activity measured with EEG has also been shown during 3-6 months poststroke (Tolonen et al., 1981; de Weerd et al., 1988; Giaquinto et al., 1994). Considerable improvements more than 1 year after the stroke are rare, but spontaneous recovery of language comprehension has been observed even 1-2 years after stroke in patients with global aphasia (Naeser et al., 1990). Furthermore, improvements in language skills after intensive therapy have been found 5-10 years after the stroke (Naeser et al., 1998; Pulvermüller et al., 2001a). Factors affecting recovery from aphasia include the initial type and degree of language impairment, age at onset, aetiology, prestroke history, and lesion location and size (Kertesz and McCabe, 1977; Demeurisse et al., 1980; Kreisler et al., 2000). Neural correlates of the process of language recovery following aphasia remain unclear. The contribution of both the left and right hemispheres to the recovery has been reported in brain-activity studies on stroke (for reviews, see Cramer and Bastings 2000; Herholz and Heiss, 2000; Rijntjes and Weiller, 2002). Several PET studies emphasize the role of left-hemisphere regions (Karbe et al., 1995, 1998; Heiss et al., 1997, 1999; Warburton et al., 1999; Rosen et al., 2000), while others have implicated the role of the right hemisphere's compensatory functions in recovering patients with aphasia (Cappa et al., 1997; Musso et al., 1999). Some functional magnetic resonance imaging (fMRI; Thulborn et al., 1999) and EEG (Papanicolau et al., 1987; Thomas et al., 1997) studies also support the contribution of the right hemisphere to recovery. Furthermore, PET (Weiller et al., 1995) and fMRI (Cao et al., 1999; Price and Crinion, 2005) studies have shown that good language recovery is associated with increased bilateral activation. Moreover, a single–photon emission computed tomography (SPECT) study by Mimura et al. (1998) suggested that left hemisphere plays a significant role in early recovery (3-9 months) from stroke, whereas for long-term language recovery (7 years) compensation by the right hemisphere appears to be important.

1.5. Event-related potentials (ERPs)

1.5.1. Exogenous P1, N1, and P2 components

ERPs are classified by their latency of occurrence (short, middle, long) and polarity (negative, positive; Näätänen, 1992). Exogenous ERPs are evoked by external stimuli and endogenous ones by internal mental processes. Long-latency responses include both exogenous (P1, N1, P2) and endogenous (e.g., MMN, N2b, P300, N400) components. The first long-latency component, P1, peaks at about 50 ms from stimulus onset and has generators in the primary auditory cortex or in its vicinity (Liegeois-Chauvel et al., 1994). The P1 is followed by an N1 wave (Näätänen and Picton, 1987), a negative deflection being maximal at the vertex of the head with a peak latency at 100 ms. The N1 is elicited by stimulus onset or when there is a fast (Näätänen and Picton, 1987) or large stimulus change, like a novel sound occurring in the stimulus sequence (Alho et al., 1998; Escera et al., 1998). The N1 amplitude is determined by the physical properties of the sounds, and it mainly reflects the activation of the auditory cortex (Näätänen and Picton, 1978; Näätänen, 1992). The N1 has subcomponents, which suggests that several different brain processes affect N1 elicitation (Hari et al., 1982; Näätänen and Picton, 1987; Alain et al., 1994; Woods, 1995). The first N1 component was suggested to reflect the activation of sensory memory (Näätänen and Picton, 1987). The N1 has a good replicability at the individual level (Pekkonen et al. 1995; Virtanen et al., 1998). The N1 is followed by a positive P2 deflection, peaking at about 180-200 ms after stimulus onset (Näätänen, 1992). The distributions of the N1 and the P2 are different, suggesting that they originate from different sources (Tarkka et al., 1995).

1.5.2. P1, N1, and P2 components in patients with brain lesions

The P1-N1-P2 complex was recorded to determine auditory processing dysfunction in patients with lesions in the auditory cortex (Perronnet and Michel, 1977; Knight et al., 1988; Leinonen and Joutsiniemi, 1989; Pool et al., 1989; Mäkelä et al., 1991; Mäkelä and Hari, 1992; Woods et al.,1993). One of these studies (Pool et al., 1989) found that the P1 response was elicited by 1000-Hz tone bursts in 9 out of 10 healthy controls, but only in 1 out of 6 patients with a left- or right-hemisphere superior temporal gyrus lesion. The magnetic N1 response elicited by noise/square-wave sequences was absent in the damaged hemisphere in 2 out of 8 patients with large temporoparietal ischaemic lesions due to a stroke in the auditory cortex, whereas small lesions or frontal lesions had no effect on N1 elicitation (Mäkelä et al., 1991). Further, left-hemisphere stroke

patients with a lesion in the temporoparietal region had reduced N1 amplitude, whereas their P2 amplitude was comparable with that of healthy subjects (Knight et al., 1980).

1.5.3. Mismatch negativity (MMN) component

Cortical sound-discrimination accuracy can be studied with the mismatch negativity (MMN) peaking at 100-250 ms after stimulus-change onset (Näätänen et al., 1978). The MMN is mainly generated in the supratemporal auditory cortex (Alho, 1995), but MMN subcomponents have also been found, for example, in the frontal areas (Giard et al., 1990; Näätänen, 1992; Rinne et al., 2000). Any discriminable change (deviant) in an ongoing homogeneous auditory stimulation (standard) elicits an MMN even when sounds are not attended (Näätänen and Picton, 1987; Näätänen, 1992, 1995; for a review, see Alho, 1995). The MMN is reliably elicited by sound-duration decrements even at the individual level (Pekkonen et al., 1995; Tervaniemi et al., 1999). Furthermore, the MMN amplitude correlates with the accuracy of the behavioural discrimination of sound change (Kujala et al., 2001a).

The MMN elicited by frequency changes mainly originates from the right hemisphere (Paavilainen et al., 1991; Giard et al., 1995; Levänen et al., 1996), whereas the MMN elicited by phonetic changes (Näätänen et al., 1997; Alho et al., 1998; Näätänen, 1999; Rinne et al., 1999; Shtyrov et al., 2000a, 2000b) or by words (Pulvermüller et al., 2001b) is predominant in the left hemisphere. These results suggest left lateralization of language-specific memory traces for speech sounds.

1.5.4. MMN in patients with brain lesions

MMN elicitation even without the subject's attention is useful in studying patient groups with speech-perception problems that can affect performance in active stimulus discrimination conditions (Näätänen, 1995). In patients with left temporoparietal damage, an attenuation of the MMN amplitude has been reported for a formant change of a synthetic vowel in speech sounds (Aaltonen et al., 1993; Csépe et al., 2001; Pettigrew et al., 2005) and for a frequency change in sounds (Alain et al., 1998; Wertz et al., 1998). Wertz et al. (1998) using right-ear stimulation found an MMN response to tone change (from 1000 Hz to 1100 Hz) in 19 out of 24 aphasic patients with lesions in the left hemisphere and in 8 out of 9 controls. For speech stimuli (from /da/ to /ga/), 13 out of 24 patients and all control subjects had an MMN. These results indicate that at least some aphasic patients have deficits in preattentive speech stimulus processing.

Moreover, the duration of the MMN to speech stimuli was significantly related to the severity of aphasia determined with the language measures (e.g., Token Test) used in that study. The authors concluded that the duration of the MMN to speech stimuli predicts the severity of aphasia. Wertz et al.'s (1998) finding was later supported by Auther et al. (2000), who studied the MMN response to changes in speech stimuli (/ga/ and /da/) in 17 aphasic patients: 9 patients with good and 8 with poor auditory comprehension abilities based on the Western Aphasia Battery (WAB; Kertesz, 1982) and Token Test total scores. An MMN was elicited only in 25% of the aphasic patients with poor auditory comprehension abilities, this being related to lesions in the temporal lobe, whereas an MMN was elicited in 89% of patients with good auditory comprehension abilities, this being related to anterior lesions that spared the temporal lobe. The authors suggested that the MMN as an index of auditory comprehension and its connection to the site of the lesion may depend on the location of the lesion in the temporal lobe.

Aaltonen et al. (1993) compared vowel and tone-frequency discrimination between 2 patients with anterior and 2 patients with posterior left-hemisphere lesions. The MMN for a vowel formant change was not elicited in patients with posterior lesions, whereas a tone-frequency change elicited an MMN in all 4 subjects. However, some other studies have demonstrated a reduced MMN for frequency changes in sounds presented to the ear contralateral to the hemisphere with temporoparietal damage (4 patients with left- and 3 patients with right-hemisphere lesions; Alain et al., 1998). These patients also had difficulties in behaviourally discriminating stimuli presented to the ear contralateral to the damaged hemisphere.

Recently, Pettigrew et al. (2005) studied MMNs to duration and frequency changes in tones and consonant-vowel changes in speech stimuli (words and non-words) in 6 aphasic patients with mild to moderate aphasia due to a left-hemisphere cerebrovascular accident. Compared with controls, patients' MMN was attenuated for a tone-duration change as well as for changes in speech stimuli. Furthermore, patients' behavioural responses to the duration, frequency, and word deviant stimuli strongly correlated with their performance in the auditory comprehension subtest of the WAB. The results also showed that both controls and aphasic patients had larger amplitude MMNs to changes in words than to changes in non-words. The authors suggested that this finding could be related to the "word advantage effect", that is, to the notion of long-term neural traces

existing for language-specific words in the brain (Pulvermüller et al., 2001b; Shtyrov and Pulvermüller, 2002; Endrass et al., 2004).

2. Aims of the study

Previous research has shown that MMN is a suitable tool for studying the brain-damaged population, since it does not depend on patients' behavioural responses. The aim of this thesis was to asses the applicability of the MMN in examining left-hemisphere stroke patients with aphasia. Neurophysiological and behavioural measures of brain function underlying auditory perception were investigated in patients and controls (Studies III-V). For this purpose, stimulus parameters and research paradigms were first developed (Studies I and II). ERPs and attentive discrimination abilities were compared between left-hemisphere stroke patients and healthy controls (Studies III and IV). Furthermore, plastic changes in the cortical substrate of auditory discrimination were evaluated by following up the evolution of MMN during recovery from a left-hemisphere stroke (Study V).

3. General methods

3.1. Subjects

The demographic data of Studies I-V are summarized in Table 2. In Studies I and II, all subjects were healthy, right-handed, and had normal hearing. In Studies III-V, subjects were right-handed, left-hemisphere stroke patients whose data were compared with those of control subjects, with the subject groups being matched by age and gender. All patients in Studies III-V had had a stroke in the left media region causing aphasia. They did not have right-hemisphere or subcortical lesions. In Study III, patients had had their stroke approximately 1.5 years and in Study IV 9.2 months prior to the investigation. In Study V, patients were followed up 4 and 10 days and again 3 and 6 months after stroke onset.

Table 2: Subject data in Studies I-V.

Study	N	Age (mean) years	Lesion location from CT and MRI scans
I	40 healthy subjects	9-84 (37)	
II	11 healthy subjects	18-29 (22)	
III	8 patients	42-62 (49)	FTA, TA,TPA, OA, FTPA
	8 controls	41-57 (48)	
IV	8 patients	42-62 (49)	FTPA, FTA
	8 controls	40-59 (48)	
V	8 patients	43-63 (55)	FTPA, FTA
	8 controls	43-63 (53)	

FTA=Frontotemporal area; TA=Temporal area; TPA=Temporoparietal area; FTPA=Frontotemporoparietal area; OA=Occipital area

3.2. ERP recording

ERP recordings in Studies I-IV were carried out in an electrically shielded room at the laboratory of the Cognitive Brain Research Unit, Department of Psychology, University of Helsinki. Study V was conducted at the Clinical Neurophysiology Department, Helsinki University Central Hospital. Methodological details of the EEG recordings are presented in Table 3. The EEG was recorded with Ag/AgCl electrodes. All EEG and EOG electrodes were referenced to an electrode attached to the nose. For subsequent analyses, the data were re-referenced either to the right mastoid (Studies I and II) or to the average of the left and right mastoids (Studies IV and V). In Study III, the signals from the left-hemisphere electrodes were re-referenced against the left mastoid, those from the midline electrodes against the average of the left and right mastoids and those from the right-hemisphere electrodes against the right mastoid in order to optimize the signal recorded from each hemisphere.

Table 3: Stimulation in Studies I-V.

Study	Component(s) of interest	Tone structure	Standard	Deviants	ISI/SOA
I	MMN	sinusoidal	75 ms	duration	300 ms ISI
II	MMN	sinusoidal	75 ms	duration; frequency	300 ms SOA
		harmonic	75 ms		
III	MMN	harmonic	75 ms	duration	300 ms SOA
	P1, N1, P2				
IV	MMN	speech	/ka/	/ko/, /kaa/	500 ms SOA
	P1, N1	non-speech	157 ms	duration; frequency	
V	MMN	harmonic	75 ms	duration; frequency	300 ms SOA

ISI: inter-stimulus interval; SOA: stimulus-onset asynchrony

Electrodes were attached in Study I to 3 (Fz, Cz, Fc) and in Study V to 9 (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4) scalp sites. In Studies II-IV, a 32-channel electrode cap was used. In all studies, the EEG sampling rate was 250 Hz. The EEG recording passband was 0.1-100 Hz, except in Study II it was 0.1-40 Hz. The filtering passband was 1-30 Hz in Studies I, III, IV, 1-10 Hz in Study II and 1-12 Hz in Study V.

During ERP recordings, subjects were requested to avoid unnecessary movements and muscle tension. They were advised not to pay any attention to the stimuli delivered via headphones (presented binaurally in Studies I, II, IV, and monaurally to each ear in Studies III and V) at an intensity of 50 dB above the individual hearing level (HL), except for Study I, in which the intensity of the sounds was at an 80 dB sound-pressure level (SPL). In Studies IV and V, subjects' hearing was tested with an automatic audiometer (Oscilla SM 950, Oriola). In Studies I and II, subjects read material of their choice, whereas in Studies III-V they watched a video without subtitles or sound during the recordings.

3.3. Data analysis

EEG epochs were separately averaged for each stimulus type. Epochs contaminated by extracerebral artefacts such as eye movements, blinking, or muscle activity (voltage variation during an epoch exceeding 150 μV in Study I and 100 μV in Studies II-V at any EOG or EEG electrode), were automatically omitted from the averages.
The peak latencies of P1 and N1 (Studies III and V) and P2 (Study III) elicited by

standard stimuli were determined from the grand-average waves as the largest positive peak (P1 30-150 ms and P2 100-200 ms), or the largest negative peak (N1 60-200 ms). The amplitude was determined from the standard stimulus responses as the average amplitude (calculated over a 10-ms time window for P1, and 30-ms time window for N1 and P2) centred around the grand-average peak latency. The MMN peak latency was separately determined for each deviant stimulus type from the grand-average difference waves (obtained by subtracting the ERP to standard stimuli from the corresponding ERP to deviant stimuli) as the largest negative peak at 100-350 ms. Thereafter, the MMN amplitude was determined from the individual difference waves as the average amplitude calculated over a 30-ms time window (20 ms in Study II) centred around this grand-average peak latency.

The statistical significance of the ERP components was evaluated with t-test by comparing the mean amplitudes with zero. Differences in ERP latency, amplitude, and scalp topography between experimental conditions and/or subject groups were statistically tested with analysis of variance (ANOVA).

3.4. Attentive stimulus discrimination

In Studies II-IV, a separate session was conducted in which subjects attentively discriminated deviant stimuli. Subjects were instructed to listen to the same stimuli used in the ERP session and to press a response key as fast and as accurately as possible whenever hearing a deviant stimulus. Responses given within time interval of 300-1200 ms (Study II), 300-900 ms (Study III) and 150-1200 ms (Study IV) from the onset of the deviant stimulus were accepted. Responses falling outside this time window were regarded as false alarms (FA). The hit rate (HR) was calculated by dividing the number of correct responses by the number of all targets. In Studies III and IV, patients' ability to understand the instructions was controlled by asking them to repeat the task (by demonstrating how the task is performed). Possible motor problems of each patient were determined, and in case the patient's preferred hand was paretic, he/she was asked to use the other hand.

3.5. Language tests

In Studies III-V, the patient's linguistic auditory performance was tested by a speech therapist with auditory subtests (word discrimination, body-part identification, commands, complex ideational material) from the BDAE (Laine et al., 1997) and with

the shortened form of the Token Test (de Renzi and Vignolo, 1962). To classify the type of language impairment, the BDAE Aphasia Severity Rating scale was used. In Study V, patients were tested by a speech pathologist at 10 days, 3 months, and 6 months after stroke onset.

4. Specific methods, results, and discussion

4. 1. Development of MMN paradigms

4.1.1. Replicability of MMN (Study I)

Study I was carried out to determine whether an MMN with a high replicability could be recorded with a short recording time. The MMN elicited by duration decrements in 40 healthy subjects was investigated.

Methods. Altogether 40 subjects (aged 9-84 years) were presented with 700-Hz tone sequences of 75 ms in duration (including 10-ms rise and fall times) and with an ISI of 300 ms binaurally via headphones. Standard tones (probability of occurrence p=0.88) were randomly replaced by occasional shorter-duration deviant tones: 25 ms or 50 ms (p=0.06/each). For 14 subjects, the recording was repeated after 2-12 weeks.

Results and discussion. In 39 of the 40 subjects, an MMN was elicited by the 25-ms deviant tone, that is, by the larger deviation (Fig. 1). The 50-ms deviant tone elicited an MMN in 32 subjects. The MMN elicited by the 25-ms deviant tone diminished with increasing age. MMN for the 25-ms deviant tone, measured on separate days in 14 subjects, was replicated in the second measurement. These results suggest that the MMN is reliably elicited in healthy subjects with the 25-ms duration deviant, promoting its usefulness in clinical settings.

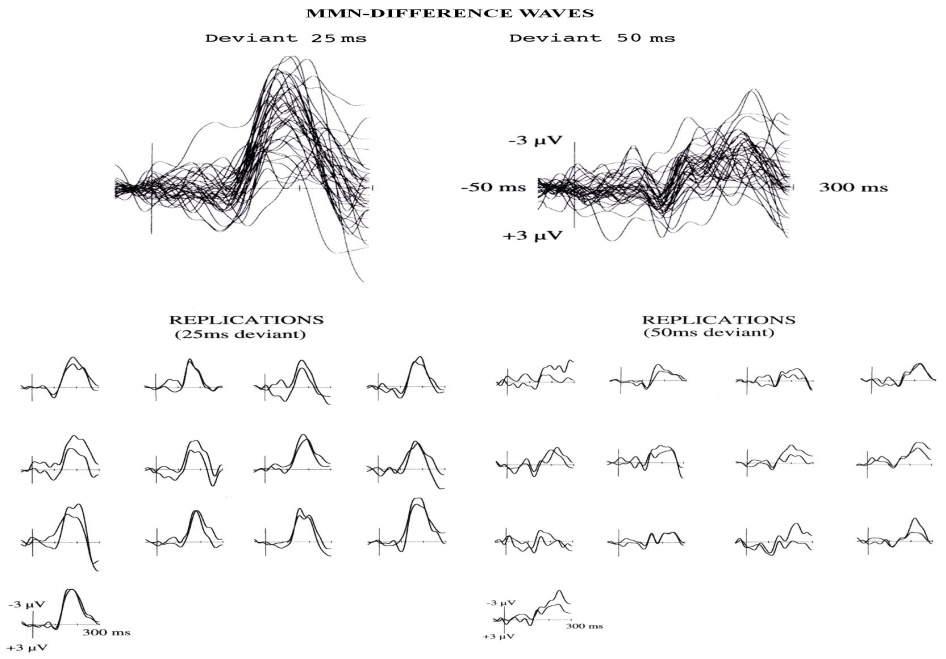

Figure 1. MMN data of Study I. **Top:** Difference waves (obtained by subtracting ERPs to standard tones from ERPs to deviant tones) from individual subjects at Fz. In 39 of the 40 subjects, an MMN was elicited by the 25-ms deviant tone (left panel). The 50-ms deviant tone evoked a detectable MMN in only 32 subjects (right panel). **Bottom:** MMN replications in 13 subjects for the 25-ms (left panel) and 50-ms (right panel) deviant tones at Fz. For the 25-ms deviant tone, the reliability of the peak amplitude was better (*r=0.36*) than for the 50-ms deviant tone (*r=-0.09*; Pearson's cross-correlation coefficient).

4.1.2. Effect of spectral tone structure on MMN (Study II)

Study II was carried out to determine whether a spectrally rich tone structure facilitates pre-attentive and attentive sound discrimination as compared with discrimination of pure sinusoidal tones in healthy adult subjects.

Methods. Eleven healthy subjects (aged 18-29 years; mean 22 years, 8 females) participated in the study. In Ignore Condition, subjects were presented with sequences of either sinusoidal tones (500 Hz) or spectrally rich tones (three frequency components: 500, 1000, 1500 Hz) of 75-ms duration (including 10-ms rise and fall times) with a SOA of 300 ms. Standard tones (p=0.76) were randomly replaced by 6 deviant tones (p=0.04/each). The deviant tones were either higher or lower (±2.5, ±5, ±10%) in frequency than the standard tone. In Discrimination Condition, the same stimuli as in Ignore Condition were presented to the subjects with a lower deviant-stimulus probability (p=0.02/each).

Results and discussion. The MMN was elicited with a larger amplitude and a shorter latency by changes in spectrally rich tones as compared with pure tones (Fig. 2). When frequency deviance was increased, the MMN amplitude was enhanced with a rich sound structure. Furthermore, behavioural responses were more accurate with large than with small deviances and with spectrally rich sounds than with pure sinusoidal tones. These results suggest that spectrally rich sound structure facilitates cortical sound discrimination. This could, at least partly, be explained by information increase with these sounds: spectrally rich tones carry more spectral (Terhard, 1974) and temporal (Schouten, 1970) information than sinusoidal tones.

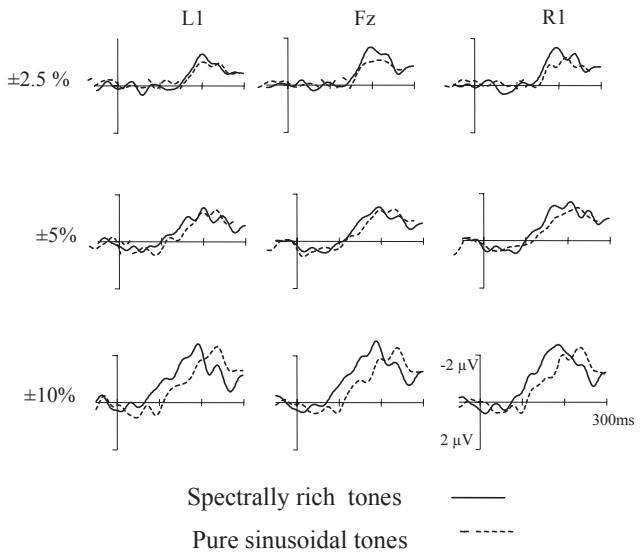

Figure 2. MMN data of Study II. MMN for spectrally rich tones (continuous line) and pure sinusoidal tones (dashed line) above the left (L1) and right (R1) frontotemporal hemispheres and at the midline (Fz). The size of the frequency change is indicated on the left. MMN elicited by deviant tones was larger in amplitude for the spectrally rich tones than for sinusoidal tones. In addition, MMN amplitude was enhanced by increased frequency change.

4.2. Studies in stroke patients with aphasia

4.2.1. Processing of duration decrements (Study III)

Study III aimed at determining pre-attentive and attentive stimulus discrimination of sound-duration decrements in left-hemisphere stroke patients with aphasic syndromes. To more precisely determine the discrimination accuracy in the left and right temporal lobes, ERPs were recorded to stimuli monaurally presented to the left and right ears in separate conditions. To compare pre-attentive processing with attentive processing, patients' ability to behaviourally discriminate deviant stimuli was investigated in a separate Discrimination Condition.

Methods. Eight left-hemisphere stroke patients (aged 42-62 years, mean 49 years; 1 female) with aphasic syndromes (7 patients with Wernicke's, 1 with global aphasia) and their age- and gender-matched controls (aged 41-57 years, mean 48 years; 1 female) participated in the study. Stimuli were monaurally presented to the left and right ears in separate conditions. This was done to stimulate primarily one hemisphere at a time (3/4 of the ascending auditory fibers project to the contralateral auditory cortex; Kelly, 1991).

The study included three conditions. In the Stimulus-Change Condition, subjects were presented with sequences of spectrally rich tones of 75-ms duration (including 5-ms rise and fall times) with an SOA of 300 ms. Standard tones (p=0.86) were randomly replaced by two occasional deviant tones, which were either 25 ms or 50 ms in duration (p=0.07/each). In the Constant-Stimulus Condition, four blocks of 150 standard stimuli with an SOA of 1075 ms were presented to subjects. The SOA was lengthened to obtain larger N1 responses. In the Discrimination Condition, four blocks of 800 stimuli with identical parameters (stimuli, SOA, intensity) as in the Stimulus-Change Condition were presented to subjects.

Results and discussion. In the Constant-Stimulus Condition, there was no significant P1 in the patient groups, the only significant P1 being found in the control group for the right-ear stimulation (Fig. 3). This suggests that a lesion in the left superior temporal area affects the P1 generators in the primary auditory cortex, in agreement with the findings of Pool et al. (1989). N1 was elicited in both groups, being significantly smaller in the patient than in the control group for right-ear stimuli over both hemispheres. These results suggest that a lesion in the posterior portion of the superior temporal gyrus weakens but does not abolish the N1 and P2 processes.

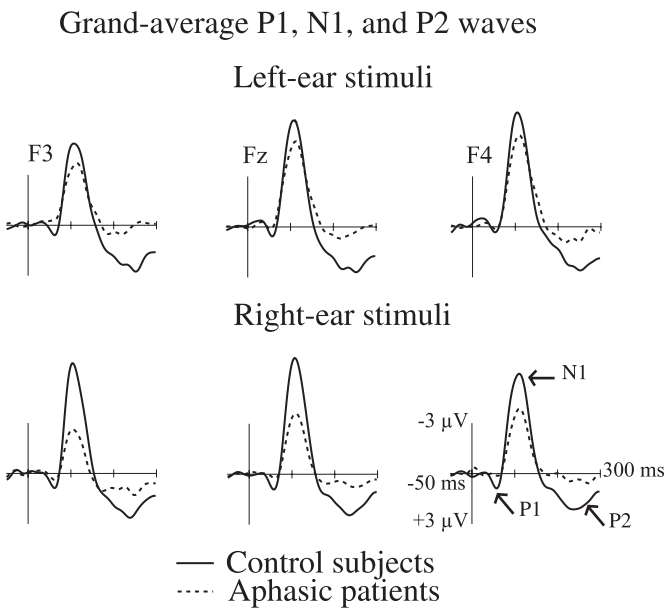

Figure 3. ERP data of Study III. The grand-average P1, N1, and P2 waves for the control subjects (continuous line) and aphasic patients (dashed line) above the left (F3) and right (F4) frontotemporal hemispheres and at the midline (Fz). ERPs to left-ear stimuli are presented in the upper panel and ERPs to right-ear stimuli in the lower panel. No P1 amplitude differences existed between the groups. N1 and P2 amplitudes differed between the groups for right-ear, but not left-ear stimuli.

The MMN for the left-ear 25-ms deviant stimuli was significantly smaller in the patient than in the control group over the left hemisphere, whereas no group differences were obtained over the right hemisphere. In contrast, when stimuli were presented to the right ear, patients had MMNs with significantly smaller amplitude than controls over both hemispheres (Fig. 4). MMNs for 50-ms deviant stimuli were small and did not differ between the groups.

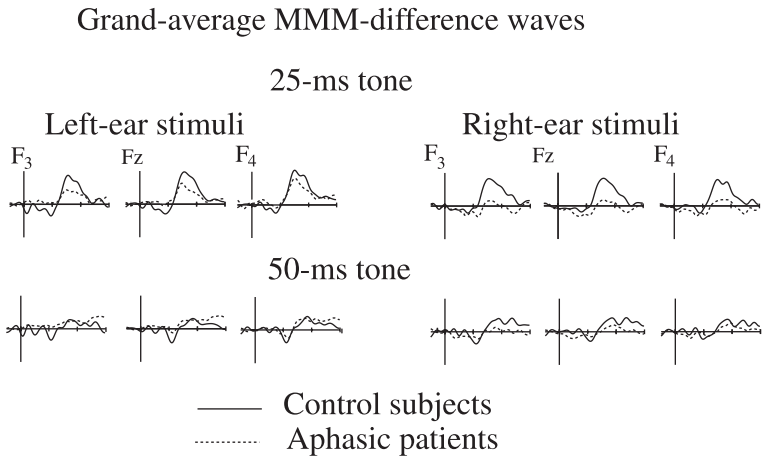

Figure 4. MMN data of Study III. MMN for control subjects (continuous line) and aphasic patients (dashed line) above the left (F3) and right (F4) frontotemporal hemispheres and at the midline (Fz). MMNs to left-ear stimuli are presented in the left panel and those to right-ear stimuli in the right panel. MMNs to the 25-ms deviant tone are presented in the upper panel and those to the 50-ms deviant tones in the lower panel. For left-ear stimuli, the MMN amplitude to the 25-ms deviant tone was significantly smaller in the patient than in the control group over the left hemisphere, whereas no differences were present between the groups over the right hemisphere. For right-ear stimuli, the MMN amplitude to the 25-ms deviant tone was significantly smaller in the patient than in the control group over both hemispheres. No group differences were obtained for the 50-ms deviant stimuli.

In the Discrimination Condition, patients detected significantly fewer deviant tones than did controls irrespective of the stimulated ear (Fig. 5).

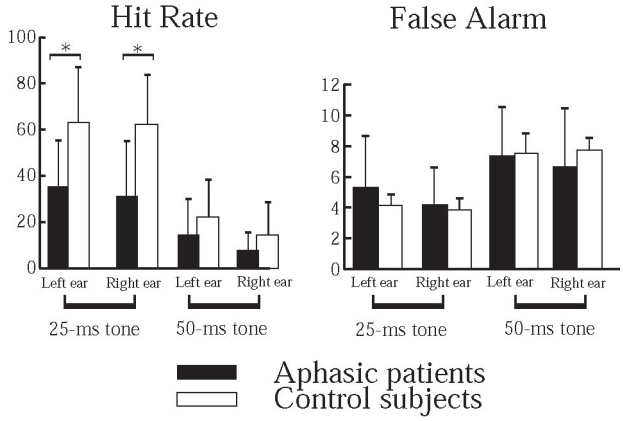

Figure 5. Behavioural data of Study III. Hit rate (HR; left panel) and false alarms (FA; right panel) with standard errors of the mean for the 25-ms and 50-ms deviant tones in the Discrimination Condition. Regardless of the stimulated ear, the aphasic patients (black bars) detected significantly fewer 25-ms tones than did the control subjects (white bars). No group differences were present in HRs or FAs for the 50-ms deviant tone, or in the FA for the 25-ms deviant tone. Significant differences are indicated with asterisks: *p<0.05, **p<0.01 (1-way ANOVA).

Differences between left- and right-hemisphere discrimination were not detected with behavioural tests in the left-hemisphere stroke patients. By contrast, the MMN results showed different effects of the lesion for left- and right-ear stimulation, suggesting that in some conditions, ERPs can be used to probe auditory-processing deficits that are difficult to evaluate with behavioural measures.

4.2.2. Processing of speech and non-speech sounds (Study IV)

Study IV aimed at determining how aphasic left-hemisphere stroke patients discriminate speech sounds and their non-speech counterparts attentively and pre-attentively as compared with healthy controls. To this end, ERPs and behavioural responses to vowel, frequency, and duration changes in speech and non-speech sounds were recorded.

Methods. Eight left-hemisphere stroke patients and their age- and gender-matched healthy controls participated. The study included two conditions. In Speech Condition, subjects were presented with sequences of Finnish syllables with an SOA of 500 ms. Standard syllables (/ka/, 157 ms in duration; p=0.8) were randomly replaced by two occasional deviant stimuli (p=0.01/each): syllable /ko/ (with changes in formants F1-F3 from 600, 1030, and 1850 Hz to 480, 860, and 2470 Hz, respectively) and /kaa/ (305 ms in duration). In the Non-Speech Condition, stimuli consisted of harmonic tones synthesized as a composite of two tones that matched the spectral harmonics in the vowel segments of the corresponding speech sounds. In the Discrimination Condition, the stimulation was identical to that used in ERP recordings but with a fewer number of trials (a total of 800 stimuli).

Results and discussion. The P1 and N1 amplitudes for the standard speech and non-speech sounds were significant in both groups, and no significant group differences were present in amplitudes or peak latencies (Fig. 6). This suggests that sound encoding was not notably impaired in our patients. Previous studies have shown that left-hemisphere lesions in the MCA region, including Heschl's gyrus, cause abnormalities in auditory processing, reflected by diminished P1 (Pool et al., 1989) and N1 (Mäkelä et al., 1991; Woods et al., 1993) amplitudes. The discrepancy between the present study and previous studies may be due to differences in lesion sizes or loci subjects or to the small number of subjects in the present study, which might diminish the statistical power.

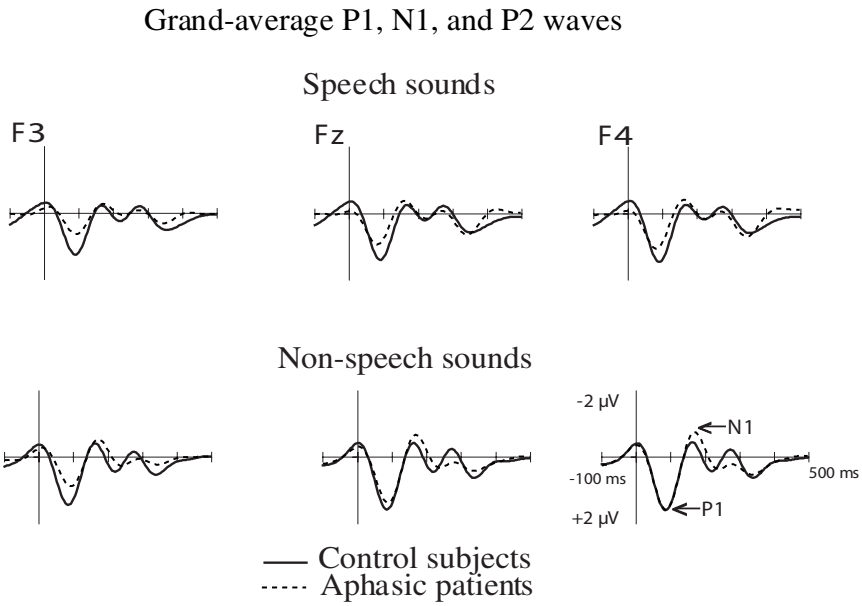

Figure 6. ERP data of Study IV. P1, N1, and P2 waves for controls (continuous line) and aphasic patients (dashed line) above the left (F3) and right (F4) frontotemporal hemispheres and at the midline (Fz). ERPs to the speech sounds are presented in the upper panel and those to non-speech sounds in the lower panel. No significant differences were present between groups in P1 or N1 amplitudes or peak latencies.

The MMN amplitude for vowel and duration changes in speech sounds was smaller in patients than in the controls (Fig. 7). For non-speech sound changes, by contrast, the MMN amplitude differences between groups were not significant. Furthermore, the MMN was significantly smaller in amplitude for speech than non-speech sounds in patients but not in controls. These results suggest that left-hemisphere lesions have differential effects on the discrimination of speech and acoustic features, indicating that they have separate neural substrates. Attenuation of the MMN amplitude for a vowel change as compared with that for a frequency change of a sine wave tone has been shown in previous studies with left-hemisphere stroke patients with aphasia (Aaltonen et al., 1993; Csépe et al., 2001). Some studies (Alain et al., 1998; Wertz, et al., 1998), have, however, reported a reduced MMN for frequency change even in sinusoidal sounds in patients with a left temporoparietal lesion. This discrepancy in results could at least partly be explained by differences in subject populations.

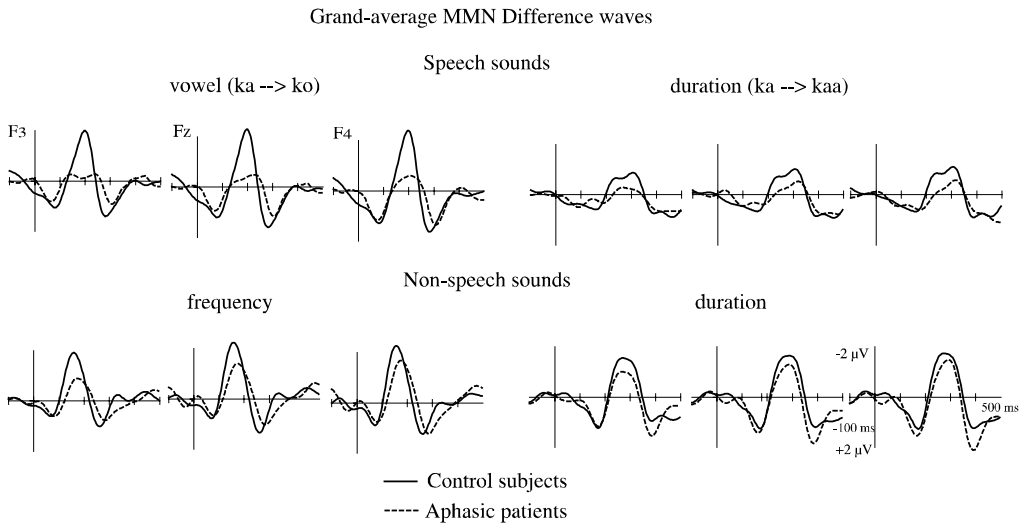

Figure 7. MMN data of Study IV. MMNs for controls (continuous line) and aphasic patients (dashed line) above the left (F3) and right (F4) frontotemporal hemispheres and at the midline (Fz). MMNs to speech sounds are presented in the upper panel and those to non-speech stimuli in the lower panel. The MMN amplitude was diminished in patients for the vowel and duration changes in speech sounds, whereas no group differences were observed for changes in non-speech sounds.

In the Discrimination Condition, patients were slower than controls in discriminating duration changes of both sound types, whereas no significant group differences were found in detecting frequency changes for either stimulus type (Fig. 8). MMN amplitude has previously been shown to be correlated with the accuracy of behavioural discrimination of sound changes in healthy subjects (Amenedo and Escera, 2000; Kujala et al., 2001b). Our results suggest that to some extent different processes are tapped with these two measures.

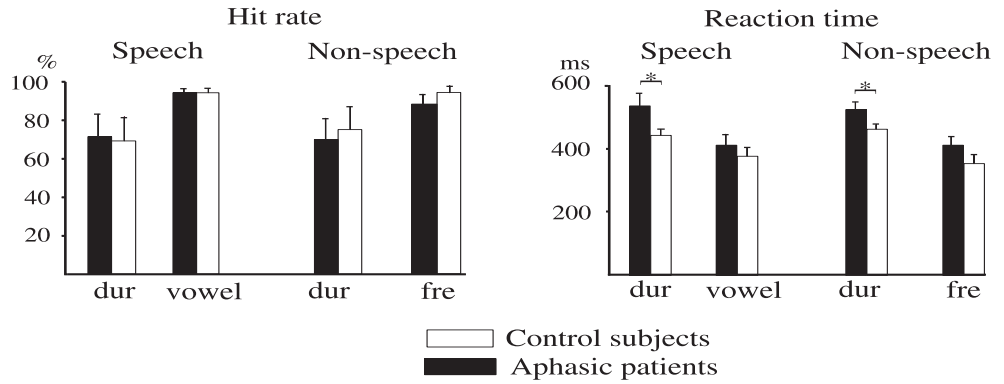

Figure 8. Behavioural data of Study IV. Hit rate (left panel) and reaction time (right panel) with standard errors of the mean for speech and non-speech sounds in the Discrimination Condition. Aphasic patients (black bars) were slower than control subjects (white bars) in detecting duration changes in both speech and non-speech sounds. There were no reaction time differences between the groups for frequency changes. Neither did the groups differ from each other in hit rate. Significant differences areindicated with asterisks: *p<0.05, **p<0.01 (1-way ANOVA).

4.2.3. Recovery of MMN (Study V)

In Study V, the time course of recovery of cortical discrimination of duration and frequency changes in aphasic left-hemisphere stroke patients was investigated to determine whether the evolution of MMN parallels with the recovery of language functions.

Methods. Eight left-hemisphere stroke patients (aged 43-63 years, mean 55 years; 1 female) were investigated 4 and 10 days, and again 3 and 6 months after the onset of their unilateral stroke. Eight age-matched healthy subjects (aged 43-63 years, mean 53 years; one female) served as controls. Subjects were presented with sequences of spectrally rich tones of 75-ms duration with an SOA of 300 ms. Standard tones ($p=0.84$) were randomly replaced by two occasional deviant tones, one of a shorter duration (25 ms; $p=0.08$) and the other of a higher frequency (including 575-, 1150-, and 1725-Hz components; $p=0.08$) than the standards.

Results and discussion. During recovery from stroke a gradual MMN-amplitude enhancement occurs (Fig. 9). This indicates that there are dynamic plastic changes in the cortical substrate of auditory discrimination. The MMN to the right-ear duration change was attenuated 4 days after the stroke. This might have been caused by an overall metabolic depression, dampening the neural processes in the affected left hemisphere, as well as brain oedema with maximal swelling occurring 3-5 days after stroke onset (Berry et al., 1957; Shaw et al., 1957; Brown et al., 1973). Reduced metabolism and blood flow in the infarcted area and diaschisis in the contralateral hemisphere are possible reasons for no change in MMN amplitude at 10 days after stroke onset.

A clear change in MMN amplitude occurred 3 months after stroke onset for the right-ear duration change. This is consisted with the results of several EEG (Tolonen et al., 1981; de Weerd et al., 1988; Giaquinto et al., 1994) and behavioural (Kertesz and McCabe, 1977; Demeurisse et al., 1980; Lenderm et al., 1985) studies showing that at 3 months after left-hemisphere stroke onset there is an enhancement in electrical activity and an improvement in language functions

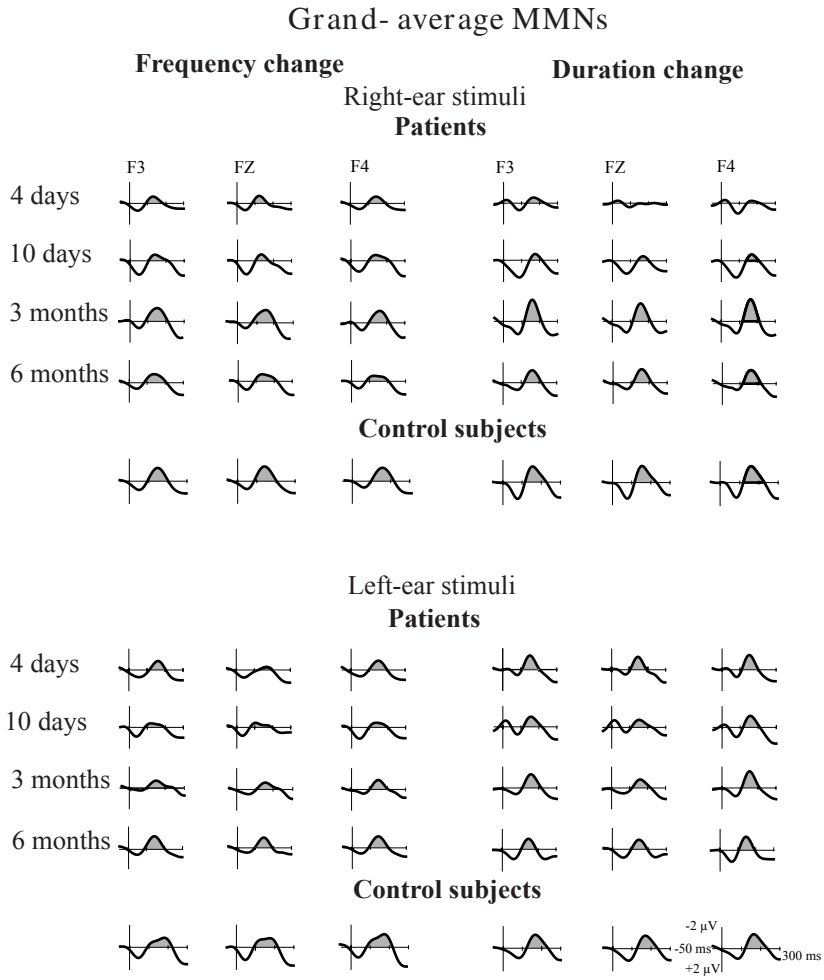

Figure 9. MMN data of Study V. Grand-average MMNs (shaded areas) to the frequency (left panel) and duration (right panel) changes above the left (F3) and right (F4) frontotemporal hemispheres and at the midline (Fz). At 4 days, patients' MMNs were attenuated for the right-ear duration change. At 10 days, MMN amplitude remained attenuated for both stimulus types, irrespective of the stimulated ear. At 3 months, MMN amplitude increased for the right-ear duration change. At 6 months, MMN amplitude for the left-ear frequency change was larger than in the other recording sessions.

At 6 months, the MMN amplitude for the left-ear frequency change was significantly larger than in the other recording sessions, suggesting a right-hemisphere contribution to the recovery. This was further supported by the result that at 6 months the MMN to the left-ear frequency change was larger than that to the right-ear frequency change. The results imply that there are different recovery times for the duration and frequency MMNs, suggesting different generators for the MMNs elicited by these sound changes. This is in agreement with the findings of previous studies (Paavilainen et al., 1991; Giard et al., 1995; Levänen et al., 1996) in healthy subjects suggesting different MMN generators for duration and frequency changes.

A significant increase was present in the Token Test scores from 10 days to 3 and 6 months and in the BDAE percentiles from 10 days to 6 months (Fig. 10), in accord with several studies showing that the recovery of language functions is most rapid during the first 3 months after a stroke (Kertesz and McCabe, 1977; Demeurisse et al., 1980; Lenderm and Lincoln, 1985; Giaquinto et al., 1994). Improvement in speech comprehension tests was paralleled by MMN amplitude enhancement at 3 months. The results showed a significant correlation between the changes in BDAE and the MMN amplitude for the duration change from 10 days to 3 months. Taken together, these findings suggest that MMN reflects dynamic plastic neural changes during recovery from stroke.

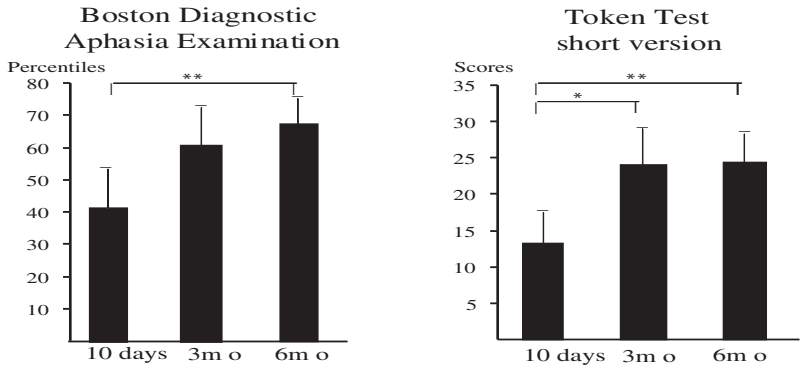

Figure 10. Behavioural data of Study V. Percentiles of the BDAE and test scores of the Token Test, with mean and SEM. There was a significant increase in BDAE percentiles from 10 days to 6 months and in Token Test scores from 10 days to 3 and 6 months. Significant differences in test scores between measurement times are indicated with asterisks: *p<0.05, **p<0.01 (1-way ANOVA).

5. General discussion

5.1. Stimulus parameters for clinical settings

Interindividual variability, replicability, and overall recording time of ERPs must be carefully taken into account when applying these methods to clinical research. In patient studies, a long data recording time and a poor signal-to-noise ratio are problematic, and several variables might affect the results, such as restlessness, fatigue, the lack of cooperation, and comprehension problems. In Studies I and II, the possible improved stimulus parameters for using the MMN in clinical studies were tested.

Study I demonstrated an MMN elicitation to large duration changes in 39 out of 40 healthy 9 to 84-year-old subjects and replication of MMN elicitation in 14 subjects

studied in two separate sessions. This is in agreement with the results of other studies (Pekkonen et al., 1995; Tervaniemi et al., 1999; Escera et al., 2000) showing that an MMN to sound-duration decrements is reliably elicited at the individual level. Study I also showed that an MMN is elicited even when stimuli are delivered with a short SOA, enabling one to keep the session duration tolerable. These results suggest that it is possible to determine reliable normal limits for the MMN to be used in clinical settings. A missing MMN or one with a very low amplitude might then indicate pathology in automatic auditory change detection.

Study II demonstrated that pitch discrimination is better facilitated with tones that are spectrally rich than with tones that are sinusoidal. The MMN amplitude was sensitive to changes in both sound structure and frequency, while the MMN latency reflected sound structure but was saturated when the magnitude of frequency change was increased. The behavioural responses were also more accurate with a larger than a smaller deviance or with spectrally rich sounds than with pure sinusoidal tones. These results suggest that as compared with pure sinusoidal tones, harmonically rich sounds facilitate sound discrimination, as reflected by the MMN and behavioural measures. According to the results of Studies I and II, the MMN provides a feasible tool for studying auditory stimulus processing in clinical populations.

5.2. Sound encoding as reflected by the exogenous P1, N1, and P2 components in stroke patients with aphasia

Results from Study III suggest that the P1, N1, and P2 elicited by sounds are distorted but not abolished by a lesion in the posterior portion of the superior temporal gyrus. No P1 was elicited in patients, whereas the right-ear stimulation elicited a significant P1 response in controls. Further, the only significant N1 and P2 amplitude differences between the groups were obtained for the right-ear stimulation. In Study IV, no significant differences were found for the P1 and N1 responses between the groups. Previous studies (Perronet and Michel, 1977; Pool et al., 1989; Knight et al., 1988; Leinonen and Joutsiniemi, 1989; Mäkelä and Hari, 1992; Woods et al., 1993; for a review, see Näätänen and Picton, 1987) have shown that left-hemisphere lesions in the MCA region including Heschel's gyrus, diminish the P1, N1, and P2 amplitudes. Differences in the stimuli used and different lesion sizes or loci between the studies could in part explain the different results. The small number of subjects in the present studies might also diminish the statistical power, resulting in insignificant effects.

5.3. Hemispheric differences in the processing of auditory information after stroke

In Study III, the hemispheric distribution of the duration MMN was abnormal in stroke patients. The MMN was bilaterally significantly smaller in amplitude in patients than in controls for stimuli presented contralaterally to the lesioned hemisphere. When the stimuli were presented ipsilaterally to the lesioned hemisphere, the MMN differed between the groups over both hemispheres. Alsi in the studies of Alain et al. (1998) and Wertz et al. (1998) reduced MMN amplitudes for frequency changes in sounds presented to the ear contralaterallyto the lesioned hemisphere were observed. Results here suggest that a lesion in the left temporal plane on the posterior portion of the superior temporal gyrus might affect the MMN generators in both hemispheres.

5.4. The Generator loci of MMN

In Study IV, the MMN was used to determine the neural basis of the processing of speech and non-speech sounds in stroke patients. The results showed that left-hemisphere lesions have differential effects on the discrimination of changes in speech and non-speech sounds, indicating different MMN generator loci for these stimuli. This was suggested by the finding that the processing of changes in speech sounds was more deteriorated than the processing of equal changes in non-speech sounds in the patient group. In the same vein, previous studies (Aaltonen et al., 1993; Csépe et al., 2001) with left-hemisphere lesion patients have shown smaller MMN amplitudes for a formant change of a synthetic vowel than for a frequency change of a sinusoidal tone.

Results from Study V indicated that the recovery of cortical frequency discrimination differed from that of duration discrimination, suggesting different generators for the MMNs elicited by these sound changes. This is consistent with findings at earlier studies (Giard et al., 1995; Levänen et al., 1996).

5.5. Recovery of the MMN after left-hemisphere stroke

Results from Study V suggest that the MMN reflects dynamic plastic neural changes during the recovery from stroke and may be associated with the alleviation of the aphasic symptoms. Thus, the MMN can be used as an indicator of cortical recovery, and the underlying plastic changes of pre-attentive auditory discrimination processes. This is in agreement with previous studies showing that the MMN reflects plastic neural changes (Näätänen et al., 1993; Kujala et al., 2001b).

For the first 4 and 10 days, the MMN amplitude was generally very low or missing. An overall metabolic depression or reduced brain metabolism and blood flow in the infarcted area as well as diaschisis in the contralateral hemisphere might explain these results. An increment of glutamatergic activity and changes in its transmitter system may be involved in MMN modulation.

The pre-attentive processing of sound changes gradually recovered, as manifested by the increased MMN amplitude at 3 months after stroke onset. Previous studies (Tolonen et al., 1981; de Weerd et al., 1988; Giaquinto et al., 1994; Cao et al., 1999; Heiss et al., 1999) have also shown increased brain activity during the first 3 months of recovery. Together with the improvement in pre-attentive sound processing, an improvement in speech understanding occurred according to the language-test performance in our study. Measurements revealed a correlation between the changes in BDAE percentiles and the MMN-duration amplitudes from 10 days to 3 months. Several clinical studies (Kertesz and McCabe, 1977; Demeurisse et al., 1980; Lenderm and Lincoln, 1985; Giaquinto et al., 1994) with language tests have demonstrated the most rapid recovery of language functions during the first 3 months after stroke onset.

Numerous studies (Weiller et al., 1995; Ohyama et al., 1996; Cappa et al., 1997; Thomas et al., 1997; Musso et al., 1999; Thulborn et al., 1999) have indicated a contralateral-hemisphere contribution to the recovery from brain lesions. The present work showed a significantly larger MMN amplitude at the 6-month session than at the other sessions to the left-ear frequency change, presumably reflecting plastic changes in the contralateral right hemisphere.

5.6. MMN and behavioural tasks

Results from Study III suggest that a left-hemisphere stroke impairs active sound-duration discrimination. However, using behavioural methods only, the differences between left- and right-hemisphere discrimination would have gone undetected.Contradicting this result, Study IV showed a disagreement between the MMN and behavioural results, suggesting that these two methods measure somewhat different processes. In Study IV, differences between the groups were found for the reaction times (RT) to duration change in complex tone and vowel, whereas the MMN amplitude was attenuated for changes in both speech and non-speech sound types. This finding stresses the importance of using a combination of measures to determine perceptual dysfunctions of aphasic patients.

6. Conclusions

The results Studies I-V suggest that

1. Automatic change discrimination in audition is impaired in left-hemisphere stroke patients with aphasic symptoms.

2. Left-hemisphere stroke also impairs active sound-duration discrimination.

3. Auditory discrimination deficits in the left versus the right temporal lobecan in some cases be more specifically determined with the MMN than by using only behavioural measures. However, the MMN and behavioural results are not always in agreement, suggesting that they to some extent measure different processes. This stresses the importance of using a combination of measures to study auditory perceptual functions.

4. Different generators exist for the MMNs elicited by speech and non-speech changes and by sound-duration and sound-frequency changes.

5. The MMN reflects the recovery of sound discrimination and the alleviation of aphasia after cortical stroke onset.

6. The MMN provides a promising tool for evaluating and following up the recovery of auditory discrimination in clinical studies.

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